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| 09/830,019 | 09/21/2001 | Chikara Aizawa | SHIM1120 | 9316 |

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| EXAMINER | |
|---|---|
| LE, EMILY M | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/830,019 | AIZAWA ET AL. | |
| | Examiner | Art Unit | |
| | EMILY M. LE | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on 03/03/2010

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,7 and 16-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7 and 16-23* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/03/10+03/10/10*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Claims*

1. Claims 22-23 are added. Claims 4-6 and 8-15 are cancelled. Claim 1-3, 7 and 16-23 are pending and under examination.

### *Claim Objections*

2. Claim 22 is objected to because of the following informalities: the recitation "heat-labile toxin or pathogenic" should be "heat-labile toxin of pathogenic". Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-3, 7, 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giuliani et al.,[1] in view of Esposito et al.[2]

In response to the rejection, Applicant argues that one of ordinary skill in the art would not be motivated to further detoxify LTR72 because Giuliani et al. teaches that it is likely that LTR72 has the appropriate safety window to be safely used in the open population, including adults and children. Applicant also argues that one of ordinary skill in the art would not have a reasonable expectation of success for arriving at the

[1] Giuliani et al. Mucosal Adjuvanticity and Immunogenicity of LTR72, a Novel Mutant of Escherichia coli Heat-labile Enterotoxin with Partial Knockout of ADP-ribosyltransferase Activity. J. Exp. Med. April 06, 1998, Vol. 187, NO. 7, 1123-1132.

claimed invention because Giuliani et al. discloses that LTK63, while nontoxic, has adjuvanticity that is inferior to that of the wildtype LT and LTR72.

Applicant's arguments have been considered, however, it is not found persuasive. Contrary to Applicant's argument, the motivation is clearly provided by Giuliani et al. Giuliani et al. establishes that LTR72 has residual toxicity. Thus, while Giuliani et al. may note that "it is likely that LTR72 has the appropriate safety window to be safely used in the open population, including adults and children", however, this statement is merely that of the opinion of the author for it is not substantiated by any data. Giuliani et al. clearly wrote that, the question is whether LTR72 mutant can be safely used in humans. [Sentence bridging pages 1128-1129, in particular.] In the instant case, it remains that rendering LTR72 nontoxic is desirable. It would have been prima facie obvious for one of ordinary skill in the art to further detoxify LTR72, thereby rendering it nontoxic for use in humans.

As for Applicant's no reasonable expectation of success argument, it is found that, contrary to Applicant's assertion, Giuliani et al. teaches that LTK63, along with LTR72, "are excellent mucosal adjuvants". [Conclusion section, page 1130, in particular.] Applicant is reminded that absolute expectation of success is not required for an obviousness rejection. The standard is reasonable expectation of success. In the instant case, Giuliani et al. clearly demonstrates that a reasonable expectation of success can readily be ascertained.

The claims are directed to a method of making a composition comprising a) purifying a toxin selected form the group consisting of pertussis toxin, heat-labile toxin of

[2] Esposito et al. Effect of Formalin treatment on electrophoretic mobility of cholera toxin. Infection and Immunity, July

pathogenic E.coli, Staphylococcus alpha and beta toxins, thermostable hemolytic toxin of Vibrio parahaemolyticus, a mutant cholera toxin, a mutant pertussis toxin, a mutant Staphylococcus alpha toxin and beta toxin, and a mutant thermostable hemolytic toxin of Vibrio parahaemolyticus, or a mutant toxin selected from the group consisting of a mutant cholera toxin, a mutant pertussis toxin, a mutant heat-labile toxin of pathogenic E. coli, a mutant thermostable hemolytic toxin of Vibrio parahaemolyticus to 95% or more purity; and attenuating the purified natural or mutant toxin by incubation in the presence of formalin at a temperature of 5° C to 40° C, wherein the purified and attenuated toxin has i) a residual toxic activity of less than 1/2000 that of the natural toxin, and an activity of enhancing production of an antibody specific to an antigen other than the attenuated toxin, and retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence, except that a formalin molecule is bound to the lysine residue of the purified and attenuated toxin. Claim 18, which depends on claim 17, requires the purified and attenuated toxin to be a mutant, wherein one or more amino acid residues are substituted, inserted, deleted or added, and having adjuvant activity, while the existing serine, glutamic acid and lysine residues are retained. Claim 19, which depends on claim 17, requires the purified and attenuated toxin retains the amino acid sequence of the natural toxin, except that a formalin molecule is bound to the lysine residue of the attenuated toxin. Claim 20, which depends on claim 17, requires the residual toxic activity be less than 1/10000 of that of the natural toxin. Claim 21, which depends on claim 17, requires that the temperature does not exceed 40 °C. Claims 1-2, 7 and 16 are directed to the composition obtained

1970, Vol. 2, No. 1, p. 120-122.

by the method of claims 17-18 and 20-21, respectively. Claim 22, which depends on claim 1, requires the purified and attenuated toxin be pertussis toxin, heat-labile toxin of pathogenic E. coli, Staphylococcus alpha and beta toxins, thermostable hemolytic toxin of Vibrio parahaemolyticus, a mutant cholera toxin, a mutant pertussis toxin, a mutant Staphylococcus alpha and beta toxins, and mutant thermostable hemolytic toxin of Vibrio parahaemolyticus. Claim 23, which depends on claim 1, requires the incubation in step (b) to be at temperature range of 5° C to 40° C.

Giuliani et al. teaches LTR72, a composition comprising a) purifying mutant heat-labile toxin of pathogenic E.coli toxin, wherein the purified and attenuated toxin has i) a residual toxic activity of less than 100,000 fold less toxic than that of the natural toxin. Giuliani et al. et al. teaches that the composition has adjuvant activity, thus, has an activity of enhancing production of an antibody specific to an antigen other than the attenuated toxin. Giuliani et al. et al. did not conduct site-mutagenesis on any serine, glutamic acid or lysine residues that is present in the amino acid sequence of the natural toxin. Hence, LTR72 retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence. LTR72 contains a substitution of Ala ==> Arg. Thus, LTR72 is a mutant, where one or more amino acid residues are substituted, inserted, deleted or added, and having adjuvant activity, while the existing serine, glutamic acid and lysine residues are retained.

Giuliani et al. did not also attenuate LTR72, which is already attenuated by substation of residue 72 from Ala ==> Arg and purified, in the presence of formalin at a temperature of 5° C to 40° C.

However, Giuliani et al. notes that LTR72, while having greatly reduced toxicity, still has a low residual level of toxicity. Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to further attenuate LTR72. At the time the invention was made, Esposito et al. teaches the detoxification of toxins using formalin at a temperature of 35°, which is between 5 °C and 40° C. Thus, it would have been prima facie obvious for one of ordinary skill in the art to combine the teachings of Esposito et al. with the teachings of Giuliani et al. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to render LTR72, an adjuvant, non toxic for pharmaceutical use. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because use of formalin around room temperature to detoxify toxins is well known in the art.

Additionally, while it is noted that Giuliani et al. purified the mutant toxin, it is not readily apparent if the purity is 95% or above. However, because Giuliani et al. does suggest the use of LTR72 as an adjuvant in pharmaceutical settings, it would have been prima facie obvious for one of ordinary skill in the art to purify LTR72 to a purity of 95% or above. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do to remove contaminants from the adjuvant to facilitate its use in a pharmaceutical setting. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the determination of a workable range, including purity level, is routinely practiced in the art.

As previously noted, MPEP § 2144.05 [R3] [II] states: Generally, differences in concentration or temperature will not support the patentability of subject matter

encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Regarding the recitation, "formalin molecule is bound to lysine residues", it should be noted that this occurs as a consequence of the formalin treatment, as Applicant discloses in the specification. In the instant case, LTR72 has lysine residues, and the treatment of formalin would necessary render the formalin molecule bound to

lysine residues. Thus, while neither the references address this, it is inherently provided by the treatment of formalin. It should be noted that the prior art does not need to appreciate this property to render the claimed invention obvious.

***Conclusion***

5. No claim is allowed.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on (571) 272-0905. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

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